REMARKS

Reconsideration and allowance are respectfully requested.

Claims 78-89, 91-94 and 98-101 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. The "compound" of the invention is restricted to a substance that has pharmacological activity against a pathogenic organism (e.g., amphotericin B). Monomeric "units" of the polymer are restricted to unit (I) or (II) for claim 78 and restricted to unit (III) or (IV) for claim 91. For the sake of convenience, the limitations of claim 90 are incorporated into independent claim 78 and claim 91 is reformatted as an independent claim. Claims 85 and 89 as presently amended combine the limitations of claims 87 and 88.

New claims 98-100 should be examined with the elected invention and species. Rejoinder of claims 94 and 101, which are drawn to methods of treatment using the elected complex, is requested upon allowance of the product claims. It is assumed that claim 91 (as well as claims drawn to pharmaceutical preparations comprising a complex as claimed in claim 91 and methods for making/using a complex as claimed in claim 91) would have to be pursued in a divisional application, but the Examiner's confirmation of this assumption would be appreciated.

35 U.S.C. 112 – Definiteness

Claims 78-88 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The limitation "polymer comprising units derived from an acrylic acid" in claim 78 was objected to by the Examiner. Incorporation of the definitions of units (I) and (II) from claim 90 moots this objection. N.B. Claim 90 was not rejected as indefinite.

The limitation "the pharmacologically active substance" in claim 83 was objected to by the Examiner. The amendment of claim 83 corrects the lack of antecedent basis.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 78-88 and 92 were rejected under Section 102(b) as allegedly anticipated by Brocchini et al. (WO 01/18080). Applicants traverse because the incorporation of the limitations from claim 90 moots this rejection. N.B. Dependent claim 90 was not rejected as allegedly anticipated by Brocchini. But Applicants disagree with what appears to be the contention in the Office Action that drug must necessarily be non-covalently associated with polymer in Brocchini's disclosure.

Brocchini discloses a polymer with narrow molecular weight distribution used to produce polymer therapeutics and pharmaceutical preparations. But all polymer/drug conjugates disclosed by Brocchini contain polymer that is covalently bonded to drug. This can be seen very clearly in the reaction scheme on page 26 of WO 01/18080, which shows the preparation of doxorubicin conjugates. It is clear from Brocchini's disclosure that only a covalently-bonded polymer/drug conjugate was envisaged: see for example, page 16, lines 9-11, "Conjugation of a bioactive agent or a derivative is carried out in a first reaction to covalently link the bioactive agent to the polymer"; page 19, line 4, "... may be covalently linked to a bioactive agent"; and page 19, lines 24-25, "The pendent chain Z may additionally be covalently bound to a ligand or bioactive agent."

In Applicants' claimed complex, the association between the polymer and the substance having pharmacological activity against a pathogenic organism is "primarily non-covalent, for example, involving any one or more of ionic, electrostatic and van der Waals forces" (emphasis added). Non-covalent association is predominant albeit there may be some covalent bonding ("Although a complex according to the present invention predominantly involves non-covalent association between the components, there may nevertheless be some covalent bonding").

These distinctions are also important in understanding the non-obviousness of the claimed invention (i.e., a complex of non-covalently associated polymer and active substance) over Brocchini (i.e., a conjugate of covalently bonded polymer and drug). Thus, this discussion is continued below with Applicants' arguments against the Section 103 rejections.

Applicants elected the species of a polymer comprising unit (I) for examination. The Examiner apparently found this species to be allowable and went on to examine the nonelected species 1 of a polymer comprising unit (II). See page 5 of the Office Action. It is respectfully requested the record be clarified in the next Official Communication that examination has proceeded to a nonelected species 1.

Applicants elected the species of amphotericin B for examination. Although the Examiner rejected claim 83, there does not appear to be any teaching in Brocchini with respect to the elected species 2 of amphotericin B. N.B. Daunomycin is elected species 3. It is also respectfully requested the record be clarified in the next Official Communication where elected species 2 is taught in the prior art.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See

id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hind-sight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 78-90 and 92 were rejected under Section 103(a) as allegedly unpatentable over Brocchini et al. (WO 01/18080). Applicants traverse.

As discussed above, Brocchini discloses a polymer/drug conjugate having covalent bonding between polymer and drug, and nothing more. Nowhere is there any suggestion that non-covalent bonding is present in Brocchini's conjugate, and certainly there are no grounds for concluding one of ordinary skill in the art would have found it obvious with a reasonable expectation of success from Brocchini's disclosure to envision a complex having non-covalently associated polymer and drug.

While the present specification states it is possible for Applicants' claimed complex to have some degree of covalent bonding, one of ordinary skill in the art would readily understand that the definition for "complex" requires primarily non-covalent association between the polymer and the active substance. Therefore, Brocchini's conjugate having covalent bonding as the predominant association between polymer and drug is clearly not encompassed by the present claims. Applicants' definition of "complex" is consistent with its art-known definition. Enclosed are Shargel et al., *Comprehensive Pharmacy Review*, at page 88:

> A complex is a species formed by the reversible or irreversible association of two or more interacting molecules or ions

and Liu, *Water-Soluble Drug Formulation*, at pages 111-112:

> A complex is a species of definite substrate to ligand stoichiometry ... Molecular Complexes: These species are formed by non-covalent interactions between the substrate and ligand ...

Applicants respectfully request that the enclosed documents be considered as evidence of the proper interpretation of the claimed "complex" as that term is consistently defined in the present specification and known in the art.

As noted above, the citation of a different nonelected species 1 on page 5 of the Office Action implies that the elected species of a polymer comprising unit (I) was found to be patentable. But clarification by the Examiner is requested. See pages 7-8 of the Office Action.

Moreover, Applicants elected amphotericin B as species 2. There is no evidence presented in the Office Action why claim 83 is not patentable over Brocchini. Nothing in the cited document appears to teach or suggest this active substance.

No reason is presented in the Office Action for modifying Brocchini's disclosure such that Applicants' claimed complex would have been obvious to one of ordinary skill in the art with a reasonable expectation of success from a conjugate having covalent bonds between polymer and drug.

For all of the above reasons, claims 78-90 and 92 are patentable over Brocchini.

Claims 78-90 and 92 were rejected under Section 103(a) as allegedly unpatentable over Brocchini et al. (WO 01/18080) in view of Kuzuya et al. (US 5,889,078) as evidenced by Junior et al. (WO 03/39435). Applicants traverse.

Brocchini's disclosure was discussed above. It only discloses covalently-linked conjugates of polymer and drug. Similarly, Kuzuya discloses a homopolymer of acrylic acid or methacrylic acid to which a physiologically active compound is covalently linked (see the general formula where R^2 is the physiologically active compound). As stated above, Applicants' claimed complex requires non-covalent association between the polymer and the active substance. Such is not disclosed by Brocchini or Kuzuya. On the contrary, it is an essential feature of the cited documents that the drug or the physiologically active compound is covalently linked to the polymer at each repeat unit.

If a modification proposed by the Examiner would change the principle of operation of the prior art invention being modified, then the cited prior art would fails to establish a prima facie case of obviousness. See *In re Ratti*, 123 USPQ 349 (CCPA 1959). Thus, the cited documents cannot be relied upon to establish a prima facie case of obviousness because their requiring covalent bonding between polymer and drug or physiologically active compound teaches against Applicants' claimed invention.

For all of the above reasons, claims 78-90 and 92 are patentable over Brocchini in view of Kuzuya as evidenced by Junior.

Claims 78-90 and 92-93 were rejected under Section 103(a) as allegedly unpatentable over Brocchini et al. (WO 01/18080) in view of Norimov et al. (Bull. Exp. Biol. Med. 111:216-218, 1991) and Kreuter et al. (Infect. Immun. 19:667-675, 1978). Applicants traverse.

Brocchini's disclosure was discussed above. It only discloses covalently-linked conjugates of polymer and drug. Similarly, Norimov and Kreuter do not change the chemical nature of the bonds between polymer and drug. As stated above, Applicants' claimed complex requires non-covalent association between the polymer and the active substance. Such is not disclosed by Brocchini, Norimov, or Kreuter. On the contrary, it is an essential feature of the cited documents that the drug is covalently linked to the polymer at each repeat unit.

If a modification proposed by the Examiner would change the principle of operation of the prior art invention being modified, then the cited prior art would fails to establish a prima facie case of obviousness. See *In re Ratti*, 123 USPQ 349 (CCPA 1959). Thus, the cited documents cannot be relied upon to establish a prima facie case of obviousness because their requiring covalent bonding between polymer and drug teaches against Applicants' claimed invention.

For all of the above reasons, claims 78-90 and 92 are patentable over Brocchini in view of Norimov and Kreuter.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Double Patenting

Claims 78-90 and 92 were rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 3-6, 8, 12, 35, 43 and 47-49 of Patent No. 6,803,438. Applicants traverse because the '438 patent claims a conjugate having covalently-linked polymer and drug. No complex as required by Applicants' claimed invention is taught or made obvious by the '438 patent.

Withdrawal of the double patenting rejection is requested.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Gary R. Tanigawa/
Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

Shargel et al.

$$mS + nL \rightleftharpoons S_mL_n \quad (1)$$

The distinction between substrate and ligand is arbitrary, and is made solely for experimental convenience. Normally, stoichiometric ratios are expressed in the order substrate:ligand, so that 1:2 stoichiometry denotes SL_2, 2:1 means S_2L, and so on.

Types of Complexes

Based on the type of chemical bonding, complexes can generally be classified into two groups (Connors 1990):

Coordination Complexes—These complexes are formed by coordinate bonds in which a pair of electrons is, in some degree, transferred from one interactant to the other. The most important examples are the metal-ion coordination complexes between metal ions and bases.

Molecular Complexes—These species are formed by non-covalent interactions between the substrate and ligand. Among the kinds of complex species included in this class are small molecule-small molecule complexes, small molecule-macromolecule species, ion-pairs, dimers and other self-associated species, and inclusion complexes in which one of the molecules, the "host", forms or possesses a cavity into which it can admit a "guest" molecule.

The classification of complexes into various types is somewhat arbitrary. They can also be classified based on the types of species involved and the nature of interaction forces (Repta 1981). Most pharmaceutically useful systems are inclusion complexes and molecular complexes between small molecules. Therefore, these will be the topic of this chapter.

Structures and Physicochemical Properties of Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of a variable number of D-glucose residues attached by α-(1,4) linkages (Clarke, Coates, and Lincoln 1988). The three most important of these are α-, β-, and γ-CDs, which respectively consist of six, seven, and eight D-glucose units. Their conformation and numbering are presented in Fig. 6.1. As a consequence of the $^4C_1$ conformation of the α-D-glucose residues and lack of free rotation about glycosidic bonds, the compounds are not perfectly cylindrical molecules, but are somewhat cone-shaped, with all of the secondary hydroxyl groups situated at one end of the annulus and the primary hydroxyl groups at the other. The cavity is lined by a ring of hydrogen atoms (bonded to C-5), a ring of D-glucosidic oxygen atoms, and another ring of hydrogen atoms (bonded to C-3), thus making the cavity relatively apolar. The shape of the molecule is stabilized by hydrogen bonds between secondary hydroxyl groups of adjacent α-D-glucose residues. The internal cavity diameters are approximately 5.7, 7-8, and 9.5 Å for α-, β-, and γ-CDs respectively. These structural features have been determined for the crys-

"Water-soluble Drug Formulation"
Liu.

6

Applications of Complexation in the Formulation of Insoluble Compounds

Wei-Qin (Tony) Tong
Glaxo Wellcome Inc.
Research Triangle Park, North Carolina

The technique of solubility enhancement by complexation has been employed for several decades. Many articles dealing with the solubilization of drug molecules through complexation have been published since the last comprehensive review on the subject over 15 years ago (Repta 1981). The interest in physical and chemical properties of inclusion complexes has grown considerably mainly due to the increased applications of cyclodextrins (CDs), cyclic carbohydrates known to form complexes with hydrophobic drugs. The objective of this chapter is to discuss some theoretical and practical considerations in applying the complexation technique to the formulation of insoluble compounds.

BACKGROUND

Definitions

A complex is a species of definite substrate (S)-to-ligand (L) stoichiometry that can be formed in an equilibrium process, in solution, and also may exist in the solid state (Connors 1990). This definition can be expressed succinctly in the following chemical equation for the formation of a complex S_mL_n.